Duke University School of Medicine

PEDIATRIC INFECTIOUS DISEASES UPDATE

DUKE CHILDREN'S Hospital & Health Center

Neonatal HSV

Recognition, Diagnosis, and Management

Coleen Cunningham MD

Important questions

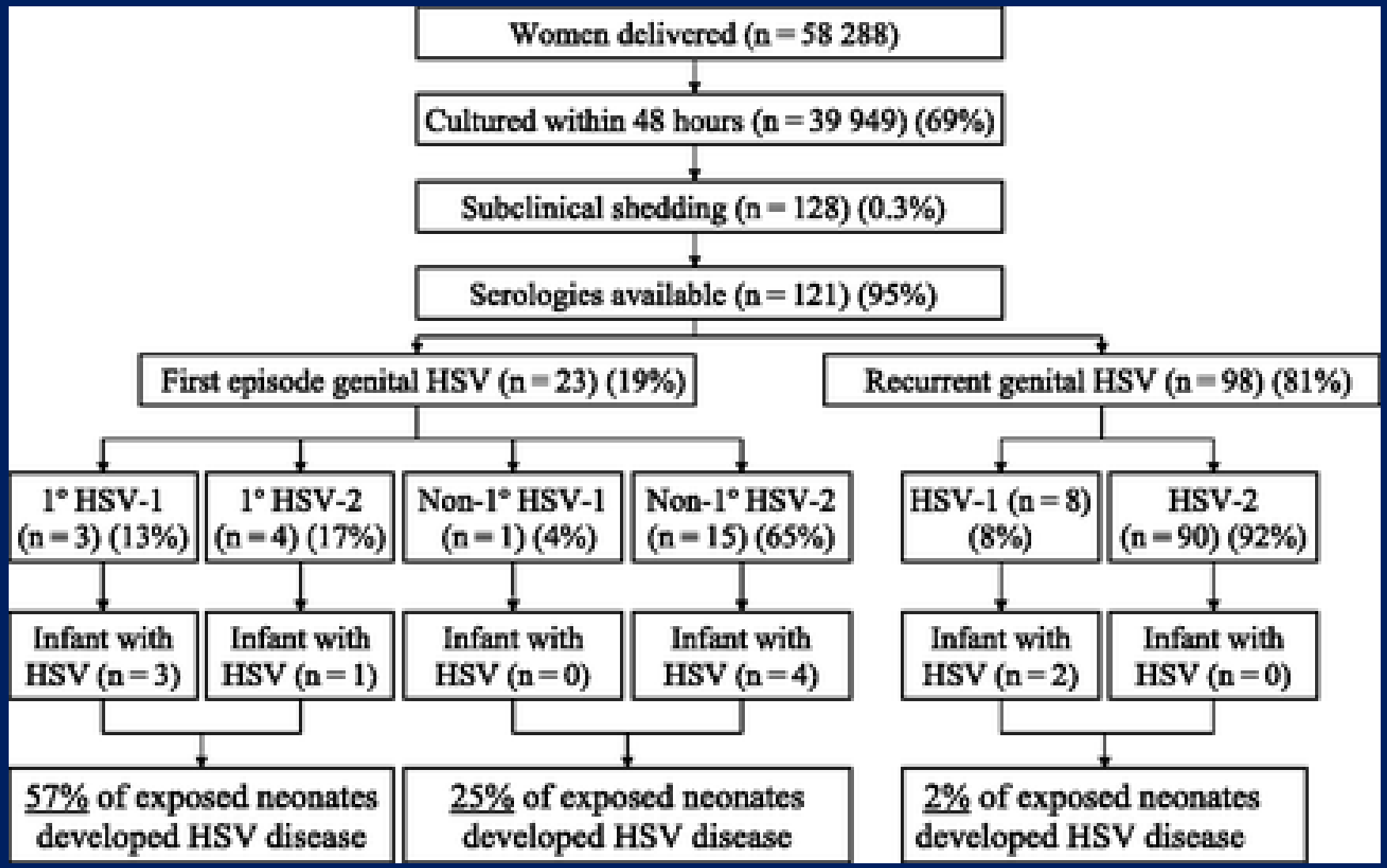
- Who is at risk?
- When do you test?
  - What tests do you perform?
- When do you treat?
- What is appropriate therapy?
  - Short term?
  - Long term?

Neonatal/Congenital HSV

- Between 8-60 cases/100,000 live births
- 1500 cases annually in the USA
  - 5% in utero
  - 85% intrapartum
  - 10% postpartum
- Poor prognosis associated with:
  - Severe symptoms at presentation
  - Delay in diagnosis
- What is the biggest risk factor for neonatal HSV?

Maternal risk factors

- Primary infection at time of delivery
- Brown et al, JAMA 2003



Congenital HSV: important points

- Symptoms begin between day 2 and day 21 in 90%
- Although rare in any group, incidence in preterm is about 2X that of term infants
- Risk of death in preterm is 4X that of term infants
- Delay in treatment is associated with increased mortality

Diagnosis

- If delay in treatment is associated with worse outcomes, how do we decide who to culture and who to treat?
- Traditionally, practitioners looked for meningitis, seizures, vesicular lesions to identify neonates for testing
- Which kids do you test for HSV?
- Which kids do you treat for HSV?
  - Age, symptoms, lab findings?

Identifying the HSV infected infant

- Of 32 cases of definite (25) or probable (7) HSV at < 60 days of life
- 88% HSV 2
- Presenting complaints:
  - Lesions- 31%
  - Seizures- 19%
  - Only NON-SPECIFIC- 50% (fever alone in 38%)
  - Non-toxic appearing- 76%

Long et al, *Pediatr Infect Dis J* 2011;30: 556–561

Presentation

- Age at onset of symptoms
  - Mean 11.6 days
  - Median 10 days
  - Range 2-35 days
- Age at presentation
  - Mean 14.6
  - Median 12 days
  - Range 4-35 days
- 90% < 21 days at symptom onset

Long et al, *Pediatr Infect Dis J* 2011;30: 556–561

Presentation- lab results

- 1/3 of patients with positive CSF PCR had <20 WBC in CSF
  - WBC in CSF were primarily mononuclear
- ½ had < 100 RBC
- 4/15 with non-specific presentation of HSV meningitis had totally normal CSF results
- "suspicious lesions" positive in 8/10
- Screening cultures positive in 6/26

Long et al, *Pediatr Infect Dis J* 2011;30: 556–561

Diagnosis in preterm infants

- Does HSV present differently in preterm vs term infants?

HSV in 12 preterm infants

- Mean GA 27.5 weeks (24.4-35)
- Seven moms had another STI during pregnancy
- Two of the moms had fever
- Only three moms had recognized history of HSV and none had lesions at delivery
- Age at onset of illness 2-13 days
- Survival in only 3/12; acyclovir dose was low, only 3 received 60 mg/kg

Pediatrics 2006; 118 (6) PPe1612-1620

HSV in preterm infants

Clinical Findings Within 1 Day of Onset of Symptomatic HSV Illness

Symptom	No. Symptomatic
Respiratory distress	12 of 12
Hypotension or poor perfusion	8 of 11
Thrombocytopenia	8 of 11
Lethargy	7 of 11
Rash	4 of 12#
Fever	2 of 12
Hypothermia	2 of 12

One additional infant developed a rash 5 days after symptom onset.

Pediatrics 2006; 118 (6) PPe1612-1620

Consider HSV

- Febrile infants 2-21 days of life
- If you are going to start IV antibiotics in this age group, consider HSV
- If considering HSV, need to perform PCR on CSF AND mucus membranes, lesions AND blood
- If considering HSV, please treat
- If child is completely better the next day, its not HSV; OK to stop ACV even if labs still pending

Delay in initiation of therapy increases mortality

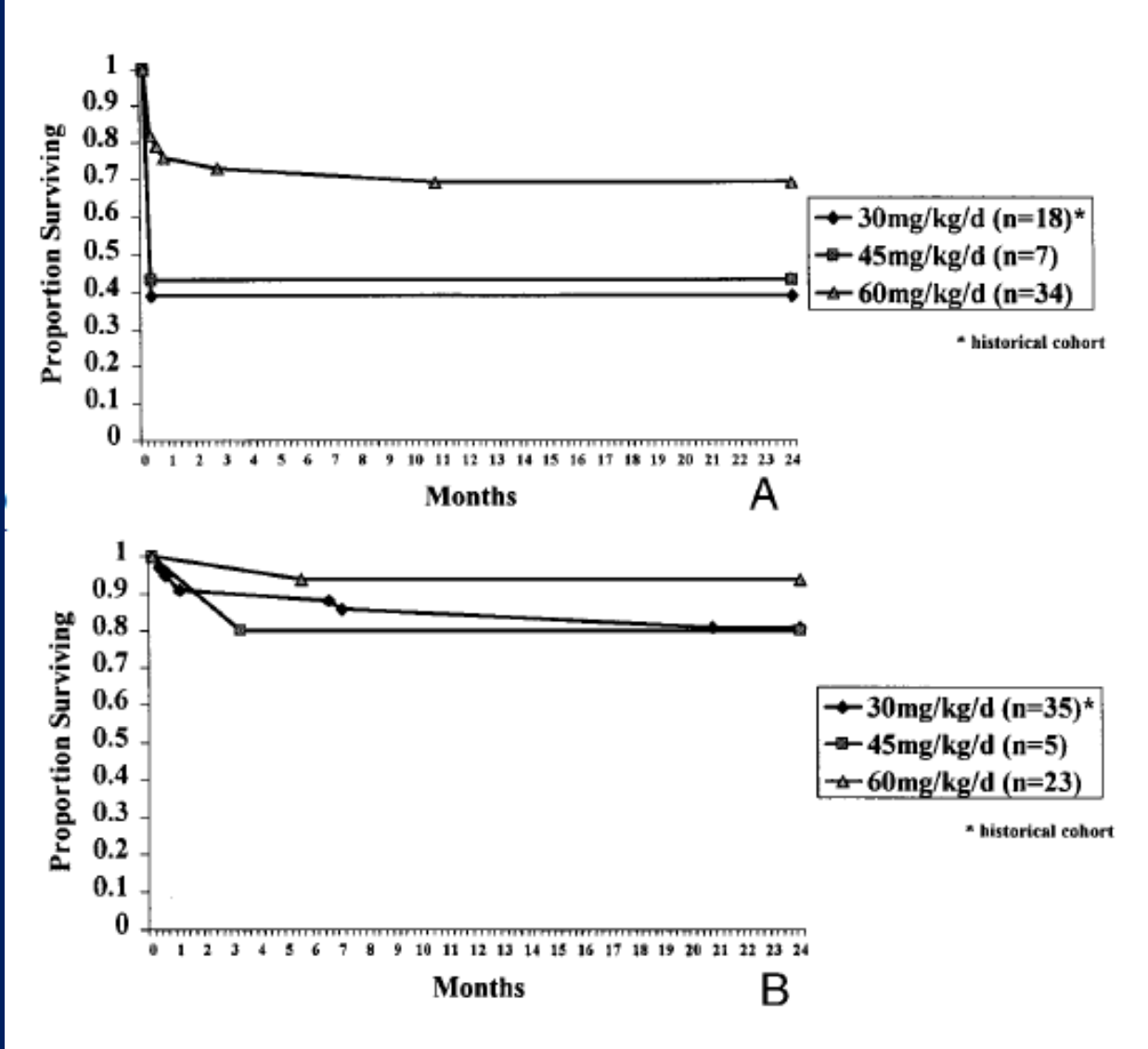
- Jan 2003- Dec 2009, 1086 neonates with HSV from 41 medical centers
- Overall mortality = 7.3%
  - Early (<1 day hospitalized) = 6.6%
  - Late(>1 day hospitalized)=9.5%
- OR for death with delay of >1 day =2.63

Shah, Pediatrics 2011; 128(6);1153-60

Initial Treatment- Acyclovir 60mg/kg better than 45 or 30 mg/kg

Disseminated disease

CNS disease

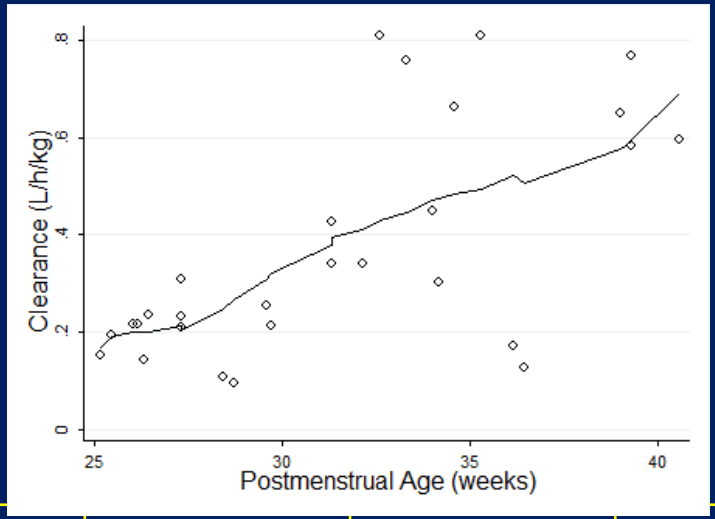


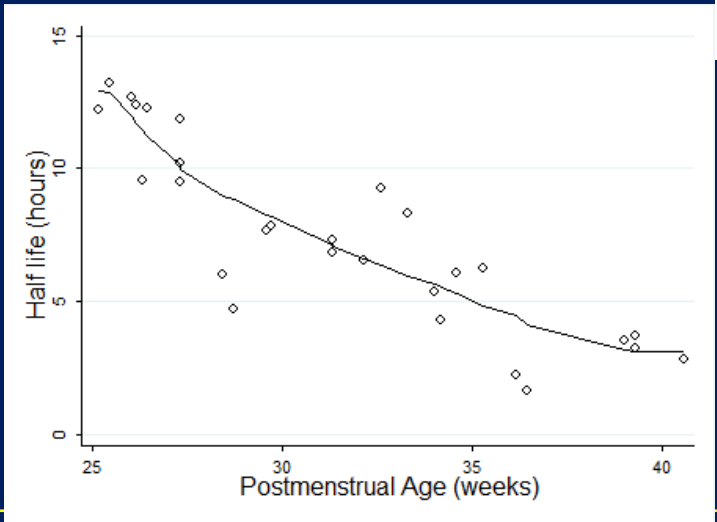
Kimberlin, 2001, Pediatrics; 108(2); 230.

Results: Comparison of Dosing Regimens

Source	Dose (mg/kg)	GA (weeks)	PMA (weeks)
FDA label	10 q8	Any	Any
Redbook and Lexicomp	20 q8	Any	Any
Harriet Lane	20 q12	<34	NA
	20 q8	≥34	NA
Neofax	20 q12	<37	<34
	20 q8	Any	≥34

Results: CL relationships





Exposures predicted using study dosing and infant PK parameters.

PMA (weeks)	N	Weight (kg)	CL (L/h/kg)	V (L/kg)	Half-life (h)	$Cmax_{ss}$ (mg/L)	$C50_{ss}$ (mg/L)	$Cmin_{ss}$ (mg/L)
<30	13	0.86 (0.578 – 1.74)	0.211 (0.095–0.310)	2.88 (0.646–5.30)	10.2 (4.73–13.2)	10.3 (4.59–110)	7.12 (3.38–65.7)	3.92 (2.38–39.3)
30– <36	9	1.77 (0.788 – 5.72)	0.449 (0.302–0.812)	4.49 (1.87–10.85)	6.55 (4.28–9.26)	8.83 (5.44–29.8)	6.80 (3.72–16.9)	5.10 (2.54–9.62)
36–41	6	3.13 (2.06 – 3.82)	0.589 (0.126–0.769)	2.55 (0.293–4.09)	3.00 (1.61–3.69)	12.4 (10.8–86.1)	5.82 (5.23–22.0)	2.90 (2.19–7.46)
Overall	28	1.37 (0.578 – 5.72)	0.278 (0.095–0.812)	3.34 (0.293–10.85)	7.07 (1.61–13.2)	11.1 (4.59–110)	6.33 (3.38–65.7)	4.15 (2.19–39.3)

Confidential data provided by Michael Cohen-Wolkowiez, M.D., PhD

CL increases with increased maturation

Conclusion of PK Study

- The population PK of acyclovir in infants shows that CL is associated with Post Menstrual Age (PMA)
- A dosing strategy based on PMA was developed for infants with relatively normal renal function
  - 20 mg/kg q12 hours in infants <30 weeks PMA,
  - 20 mg/kg q8 hours in infants 30 to <36 weeks PMA
  - 20 mg/kg q6 hours in infants 36 to <41 weeks PMA
- This dosing would achieve the surrogate efficacy target in >90% of infants

HSV resistant virus

- Frequently develops in immunocompromised, especially those on oral acyclovir. Uncommon in normal host.
- Recent report of increase resistance in HSV Keratitis
- Alternative agents to consider
  - Foscarnate
  - Cidovovir
  - CMX001

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Original Article

Journal of Perinatology 2005; 25:156–161

Improved Neurodevelopmental Outcomes following Long-Term High-Dose Oral Acyclovir Therapy in Infants with Central Nervous System and Disseminated Herpes Simplex Disease

K.F. Tiffany, MD
D.K. Benjamin, Jr, MD, MPH, PhD
P. Palasanthiran, MD
K. O'Donnell, PhD
L.T. Gutman, MD

children had brief recurrences of dermal lesions, and none had evidence of neurologic deterioration. There were no serious or sustained adverse drug reactions.

CONCLUSION:

This pilot study reports improved outcomes in a small cohort of infants

- 16 infants enrolled and followed through 2 years of age
- 12/16 with CNS involvement
- All treated with 1500 mg/m2/day for 21 days
- All started on oral acyclovir 1500 mg/m2/DOSE bid

Table 3 Neurodevelopmental Follow-Up

	All children	
	Mental	Motor
Number of patients in category	16	14
Bayley scale score		
Accelerated (>115)	1	0
Within normal limits (85–114)	10	11
Mild delay (70–84)	4	0
Significant delay (<69)	1	3

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

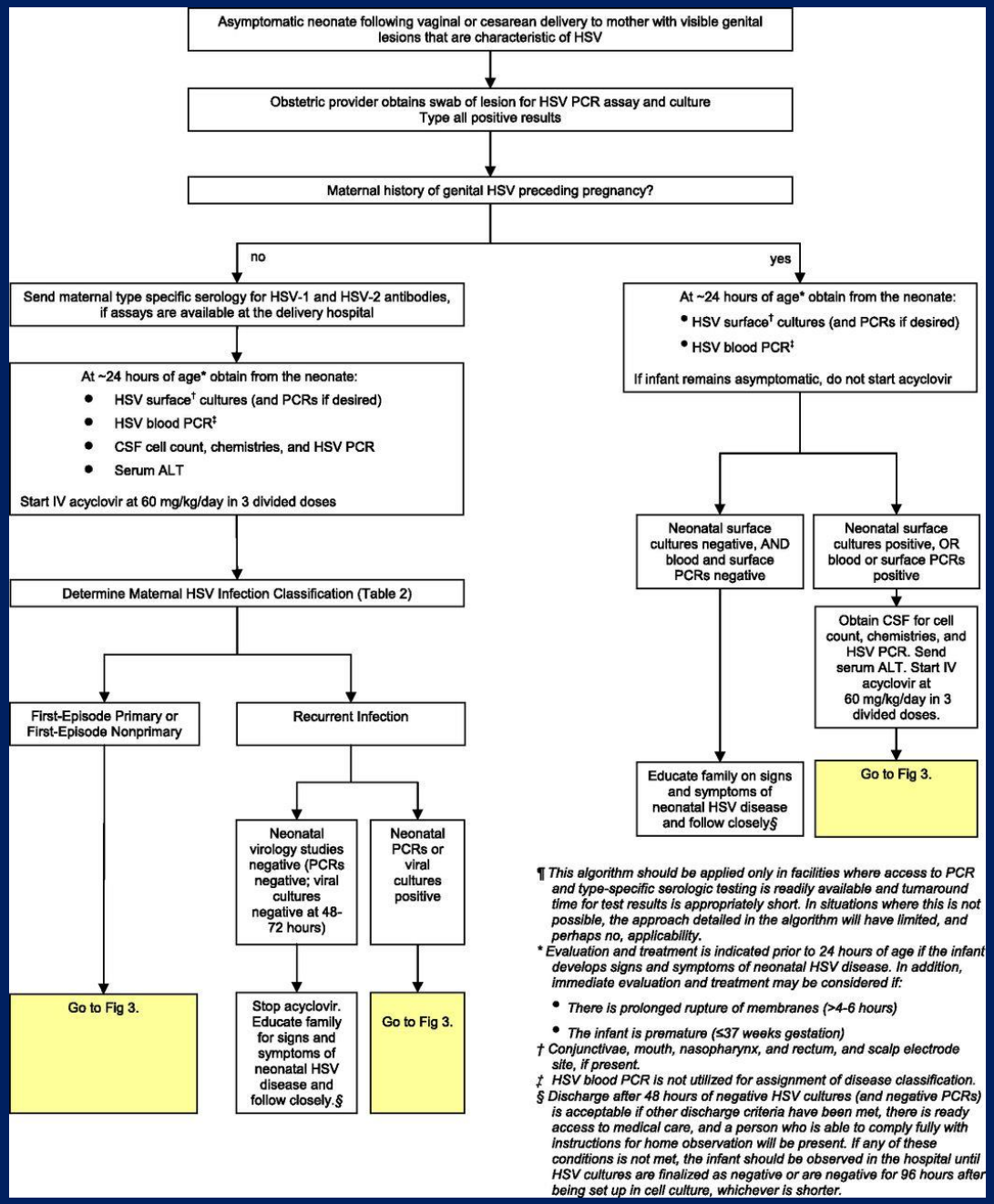
Oral Acyclovir Suppression and Neurodevelopment after Neonatal Herpes

David W. Kimberlin, M.D., Richard J. Whitley, M.D., Wen Wan, Ph.D., Dwight A. Powell, M.D., Gregory Storch, M.D., Amina Ahmed, M.D., April Palmer, M.D., Pablo J. Sánchez, M.D., Richard F. Jacobs, M.D., John S. Bradley, M.D., Joan L. Robinson, M.D., Mark Shelton, M.D., Penelope H. Dennehy, M.D., Charles Leach, M.D., Mobeen Rathore, M.D., Nazha Abughali, M.D., Peter Wright, M.D., Lisa M. Frenkel, M.D., Rebecca C. Brady, M.D., Russell Van Dyke, M.D., Leonard B. Weiner, M.D., Judith Guzman-Cottrill, D.O., Carol A. McCarthy, M.D., Jill Griffin, R.N., Penelope Jester, R.N., M.P.H., Misty Parker, M.D., Fred D. Lakeman, Ph.D., Huichien Kuo, M.S., Choo Hyung Lee, M.S., and Gretchen A. Cloud, M.S., for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group

- Enrolled infants with SEM or CNS disease
- Randomized to oral ACV 300 mg/m2/dose q8h for 6 months or placebo

- 28 of 45 infants in the CNS disease group had Bayley Scales of Infant Development at 12 month of age. Those randomized to receive acyclovir had significantly higher mean
- Bayley mental-development scores at 1 year (88.24 vs. 68.12, P = 0.046).
- They did not see a difference in scores for children with SEM only disease.

Algorithm for the evaluation of asymptomatic neonates after vaginal or caesarean delivery to women with active genital herpes lesions.



Kimberlin D W et al. Pediatrics 2013;131:e635-e646

PEDIATRICS

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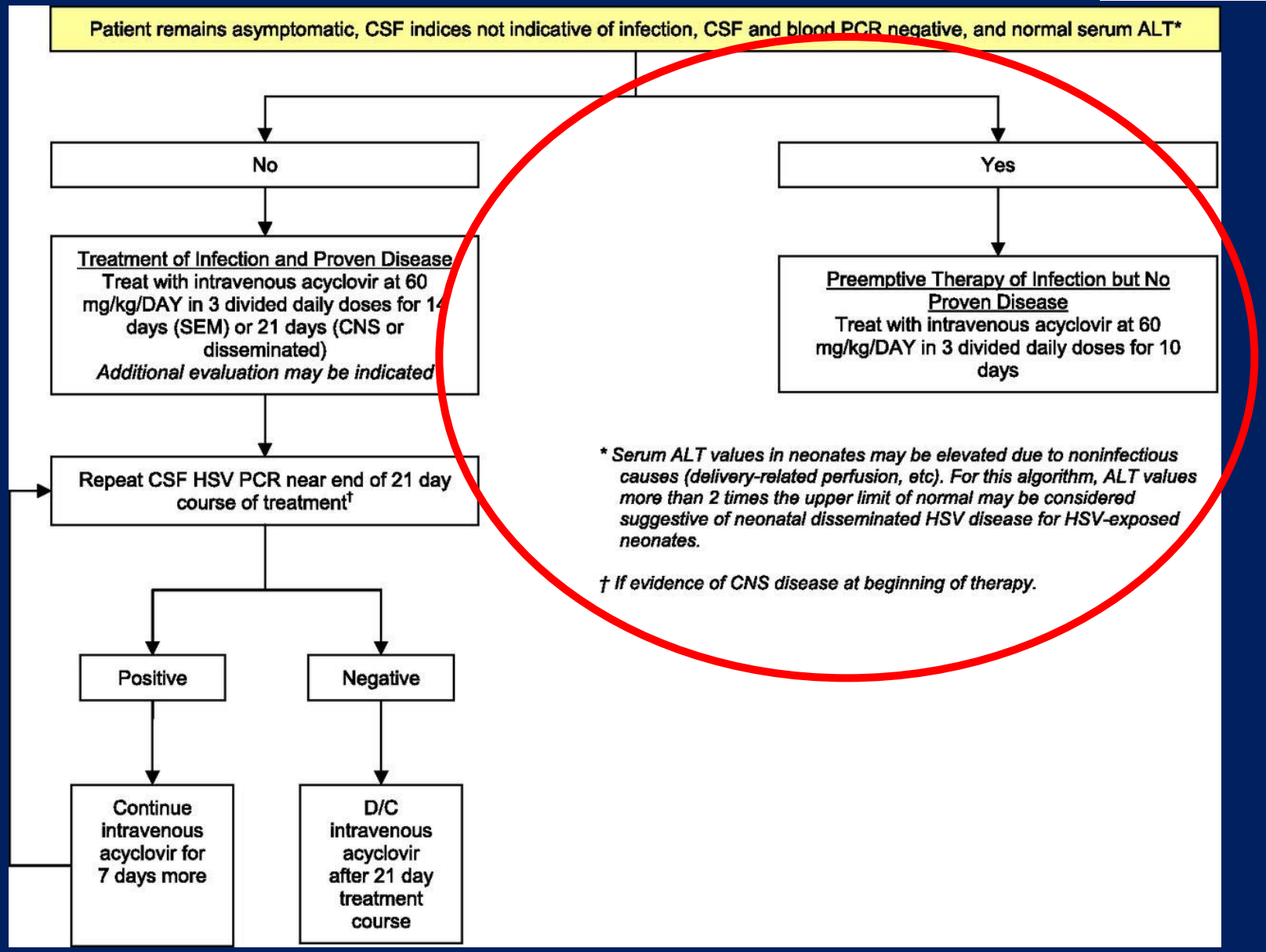

Kimberlin D W et al.
Pediatrics
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PEDIATRICS

Therapy for Congenital HSV

- IV ACV for 2 weeks for SEM, 3 weeks for disseminated or CNS
- After documented negative LP, change to oral 1500 mg/m2/DOSE bid for 2 years
- Refer to Peds ID for follow up and monitoring

Now that you have the data

- Who will you test for HSV?
- Who will you treat?
- What drug and dose will you use?
- How long will you treat?

HSV summary

- AAP recommendations for management of infants born to women with primary disease
- Consider diagnosis in all "R/O sepsis" term infants between day 2-21 (28) of life
- Consider diagnosis in all preterm infants with unexplained respiratory deterioration between day 2 and 28 of life
- Before starting ACV, obtain PCR on:
  - Blood, lesions, mucosal surfaces and CSF
  - In preterm infants, include ET PCR
- If considering dx, start empiric ACV

Common Problem Scenarios

- 10 day old with fever, no skin lesions, LP normal with negative CSF PCR for HSV, no other testing done. On ACV for 48 hours. What do we do now?
- 14 day old, all appropriate testing sent (blood, mucus membranes and CSF) and now afebrile, feeding well and back to baseline at 48 hours. Ready to go home but blood PCR not back yet. What to do?
- 7 day old admitted with fever, no risk factors for HSV, started on IV antibiotics but no ACV and no viral testing. Liver enzymes elevated. What to do?